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Bernstein

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[54] **SOLID PHARMACEUTICAL COMPOSITIONS FOR THE ORAL ADMINISTRATION OF GALLIUM**

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[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **09/015,425**

[22] Filed: **Jan. 29, 1998**

Related U.S. Application Data

[62] Division of application No. 08/956,175, Oct. 22, 1997, which is a continuation of application No. 08/655,220, Jun. 5, 1996, abandoned, which is a continuation of application No. 08/505,037, Jul. 21, 1995, Pat. No. 5,574,027, which is a continuation of application No. 08/309,624, Sep. 21, 1994, abandoned, which is a continuation of application No. 08/104,623, Aug. 11, 1993, abandoned, which is a continuation of application No. 07/782,434, Oct. 25, 1991, Pat. No. 5,258,376, and a continuation-in-part of application No. 07/656,016, Feb. 14, 1991, abandoned, which is a continuation of application No. 07/440,277, Nov. 22, 1989, abandoned.

[51] **Int. Cl.**[7] **A61K 31/555**

[52] **U.S. Cl.** **514/184**; 549/210

[58] **Field of Search** 514/184; 549/210

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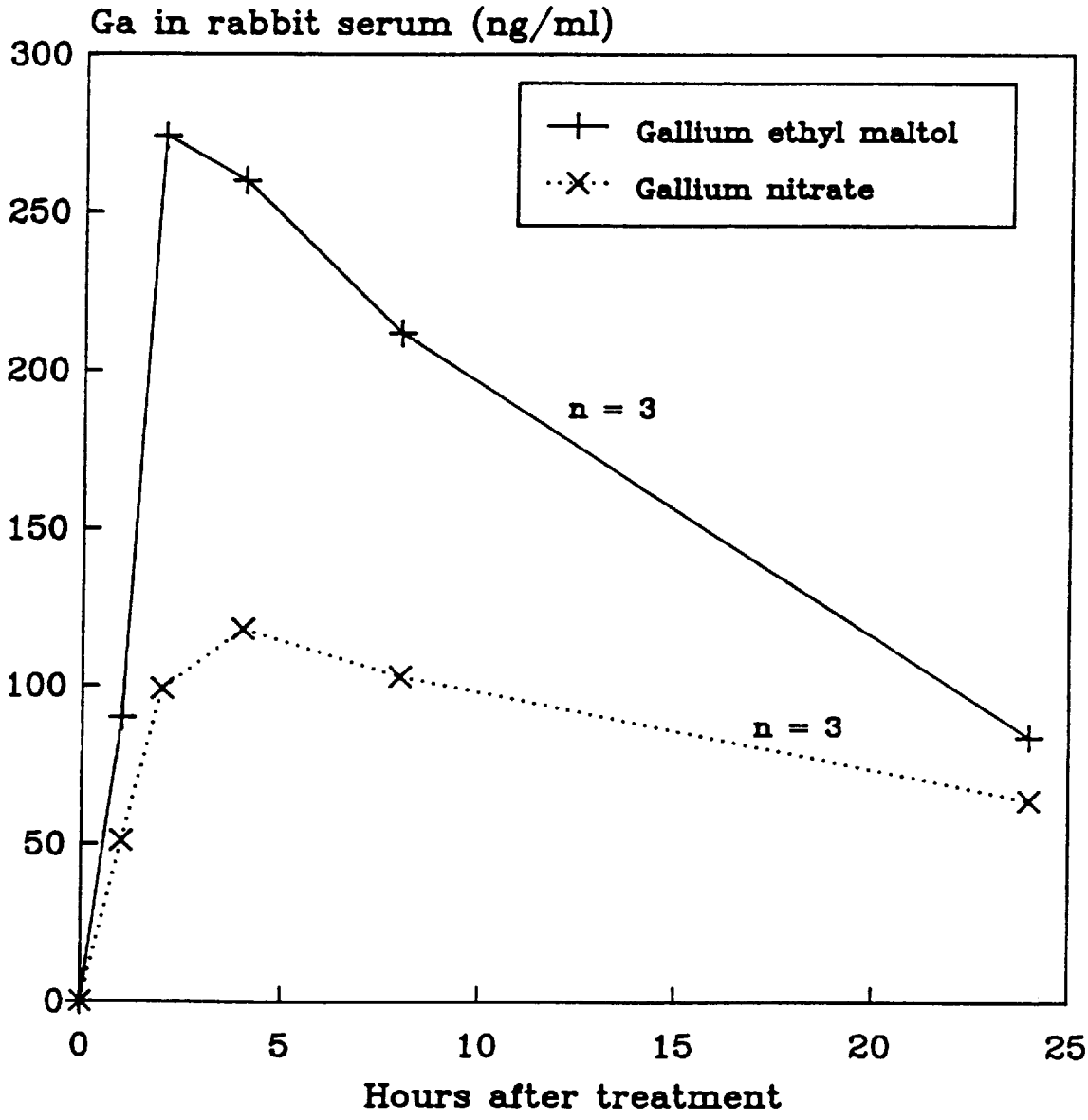
[57] **ABSTRACT**

The subjects of this invention are pharmaceutical compositions that comprise gallium complexes of 3-hydroxy-4-pyrones. The compositions have been developed to provide pharmaceutically acceptable gallium bioavailability together with low toxicity, particularly for oral administration. Compositions included in this invention should be useful in providing gallium to humans and other animals for a wide variety of medical and veterinary applications, including the treatment, prevention, or diagnosis of certain bone diseases, certain cancers, and certain disorders of calcium homeostasis.

11 Claims, 1 Drawing Sheet

Figure 1. Results of preliminary gallium bioavailability study on gallium ethyl maltol complex.



SOLID PHARMACEUTICAL COMPOSITIONS FOR THE ORAL ADMINISTRATION OF GALLIUM

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a divisional of U.S. Ser. No. 08/956,175, filed Oct. 22, 1997, allowed, which was a continuation of U.S. Ser. No. 08/655,220, filed Jun. 5, 1996, abandoned, which was a continuation of U.S. Ser. No. 08/505,037, filed Jul. 21, 1995, now issued as U.S. Pat. No. 5,574,027, which was a continuation of U.S. Ser. No. 08/309,624, filed Sep. 21, 1994, abandoned, which was a continuation of U.S. Ser. No. 08/104,623, filed Aug. 11, 1993, abandoned, which was a continuation of Ser. No. 07/782,434, filed Oct. 25, 1991, now issued as U.S. Pat. No. 5,258,376, which was a continuation-in-part of U.S. Ser. No. 07/656,016, filed Feb. 14, 1991, abandoned, which was a continuation of Ser. No. 07/440,277, filed Nov. 22, 1989, abandoned.

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FIELD OF THE INVENTION

The invention comprises gallium compositions for pharmaceutical use. These compositions provide pharmaceutically acceptable gallium bioavailability, and are particularly useful for oral administration. Gallium is potentially of great pharmaceutical value for the treatment and prevention of many human and animal diseases, including hypercalcemia, cancer, and especially certain widespread degenerative bone diseases such as osteoporosis and Paget's disease.

BACKGROUND

Gallium is known to accumulate in certain tumors, inflamed tissue, and bone tissue by mechanisms that are largely unknown. Binding of gallium to transferring, particularly lactoferrin, is thought to be responsible for some of the transport of gallium in the body, and for the concentration of gallium in certain tumors and inflamed tissues. Radioactive ^{67}gallium citrate compositions are used in patients to diagnose certain malignancies and infections, including those in bone tissue. Non-radioactive gallium compositions, and compositions containing other Group IIIa

elements, have been found effective in treating some tumors in animals and humans. Gallium is thought to be the least toxic and most effective of these Group IIIa elements (Hart and Adamson, 1971). U.S. Pat. No. 4,596,710 discloses an anticancer treatment that uses gallium chloride. The gallium ion itself appears to be the active agent; the form in which the gallium is administered (e.g. as the nitrate, sulfate, or chloride) does not appear to affect its activity (Adamson et al., 1975).

Gallium appears particularly promising for treating and preventing hypercalcemia and certain bone diseases. Treatable bone diseases include such widespread conditions as osteoporosis, osteopenia, Paget's disease, malignant bone disease, and other conditions associated with increased bone resorption in humans or animals. U.S. Pat. Nos. 4,529,593 and 4,704,277 disclose treatments using gallium salts, preferably gallium nitrate, for regulating the resorption of calcium from bone in certain bone diseases and hypercalcemia, and for increasing the mass and tensile strength of bone.

If gallium is to be used as a treatment for widespread, chronic conditions such as osteoporosis (which affects over twenty million people in the United States), an oral form of gallium is needed that is safe and has high bioavailability. The currently preferred form of gallium (a composition containing mostly gallium nitrate) is absorbed from the gastrointestinal tract of dogs into blood serum in the amount of only 0.5–2% from an orally administered dose (U.S. Pat. No. 4,529,593). The percent absorption from other simple gallium salts is not likely to be significantly different, as such salts dissociate in aqueous solutions to produce mainly trivalent gallium ions, which appear to have very low absorbability from mammalian gastrointestinal tracts. The very low observed bioavailability may not be acceptable for an orally administered drug.

The compositions included in this invention were developed to provide sufficiently high gallium bioavailabilities, especially when administered orally, to be pharmaceutically acceptable for providing gallium to humans and animals.

SUMMARY OF INVENTION

The subjects of this invention are pharmaceutical compositions that comprise gallium complexes of 3-hydroxy-4-pyrones, and some methods for producing them. The invention is designed to provide pharmaceutically acceptable gallium bioavailability with low toxicity, particularly for oral administration. Compositions included in this invention should be useful in providing gallium to humans and other animals for a wide variety of medical and veterinary applications, including the treatment, prevention, or diagnosis of certain bone diseases, certain cancers, and certain disorders of calcium homeostasis.

BRIEF DESCRIPTION OF THE FIGURE

FIG. **1** is a graphical representation of the data given in Table 1, showing a comparison of the absorption of gallium into blood serum from gallium ethyl maltol suspension versus gallium nitrate solution, by oral administration to rabbits. Details of the experiment are given in the section entitled Example 2, which follows. Due to uncertainties in the measurement of gallium in serum, the relative proportions of gallium in the samples are more significant than the measured concentration values themselves.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

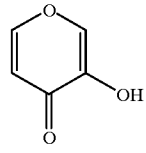
The following particulars of the invention describe some preferred aspects thereof. These particulars, however, do not

indicate any limitations to the invention, but are only examples of particular, preferred embodiments.

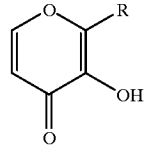
The invention comprises any and all pharmaceutical compositions that comprise a gallium complex or gallium complexes of 3-hydroxy-4-pyrone wherein from none through three of the hydrogen atoms attached to ring carbon atoms are replaced by a hydrocarbon group of from one through six carbon atoms. Such complexes, and the crystalline and non-crystalline solids and fluids, including solutions, that contain them are believed to be wholly new, as no prior reference to them can be found. Such complexes are, however, believed to be analogous in many respects to similar complexes of iron, as described, for example, in U.S. Pat. No. 4,575,502. It is noted that very few gallium analogs of iron compounds are known. Some of the iron complexes are reported to provide high oral bioavailability of iron, and some are used as dyes (U.S. Pat. No. 4,575,502).

The unsubstituted form of 3-hydroxy-4-pyrone (also called pyromeconic acid) contains three hydrogen atoms that are bound only to ring carbon atoms (Formula 1). Any combination of these

Formula 1



Formula 2



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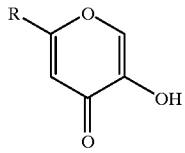

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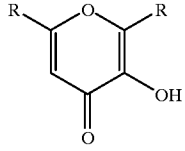
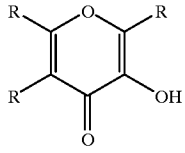


Formula 5



three hydrogen atoms can be replaced by a hydrocarbon group; all such substituted compositions are included in the invention. The locations of a few possible substitutions are presented in Formulas 2–5, in which R is a hydrocarbon group (including ethyl, methyl, isopropyl, and n-propyl groups); many others are also possible. The hydrocarbon groups are preferably acyclic and are preferably unbranched. Groups containing six or fewer carbon atoms, particularly of one through three carbon atoms, especially methyl or ethyl, are preferred. One substitution is preferred; a substitution at either the 6-position or especially the 2-position is preferred. Some examples of specific compounds whose gallium complexes may be used in compositions comprised by the invention are: 3-hydroxy-2-methyl-4-pyrone (Formula 2, R=CH_3; also called maltol, larixinic acid) and 3-hydroxy-2-ethyl-4-pyrone (Formula 2, R=C_2H_5; also called ethyl maltol, ethylpyromeconic acid), both of which are of the most interest; 3-hydroxy-4-pyrone (Formula 1; also called pyromeconic acid); and 3-hydroxy-6-methyl-4-pyrone (Formula 3, R=CH_3). The neutral complex of hydroxypyrone:gallium in 3:1 molar proportion is preferred.

This invention includes methods for the preparation of gallium complexes of 3-hydroxy-4-pyrone or 3-hydroxy-4-pyrones wherein from one through three of the hydrogen atoms attached to ring carbon atoms are replaced by a hydrocarbon group containing from one through six carbon atoms. Such methods comprise reacting such hydroxypyrones with gallium ions and isolating, at least in part, the resulting complex or complexes.

Certain of the 3-hydroxy-4-pyrones occur naturally and may be obtained by extraction from the natural sources. For example, maltol is found in the bark of the young larch tree (*Larix decidua* Mill.), and in pine needles, chicory, wood tars and oils, and roasted malt (Windholz et al., 1976). Certain of the 3-hydroxy-4-pyrones are available commercially, including maltol and ethyl maltol. Others can be made from pyromeconic acid as a starting material, which can be derived from the decarboxylation of meconic acid. It is noted that maltol and ethyl maltol are in widespread use as flavoring and fragrance-enhancing agents for foods, and have very low toxicities when taken orally.

The gallium complexes can be prepared by the reaction of gallium ions and 3-hydroxy-4-pyrones in solution. Gallium ions can be derived from a gallium salt, such as a gallium halide, particularly gallium chloride, or a gallium nitrate compound, especially a hydrated gallium nitrate. The gallium nitrate compounds are often preferable as they are easier to work with than gallium halides, which may be highly irritating and may react violently with many solvents, including water. Using the proper safeguards, a variety of gallium salts can be used. The reaction is conveniently effected in a mutual solvent, including but not limited to mixtures containing water, ethanol, methanol, and chloroform. Pure water may be used in many cases, though the purification of the gallium hydroxypyrone complexes may be difficult if it is used. A preferable method, if it is desired to separate at least a major part of reaction by-products such as sodium nitrates, sodium chloride, and sodium carbonates, is to use a mixture containing roughly equal parts of ethanol and chloroform, with a trace of water. The reaction by-products mentioned above have very low solubilities in this mixture and can be removed readily by filtration.

To produce the preferred neutral 3:1 hydroxypyrone:gallium complex, the hydroxypyrone and the gallium ions are mixed in 3:1 molar proportions, preferably with a slight excess of hydroxypyrone to insure a great preponderance of the 3:1 complex over the 2:1 and 1:1 complexes. The proportions of the particular complexes formed are dependent upon the pH of the solution. When a gallium salt such as a halide or nitrate is dissolved, the resulting solution will generally have a low pH. To form a preponderance of the preferred neutral 3:1 complex, a pH of from 5 to 10, preferably 7 through 8, is used. If a more acidic solution is used, a preponderance of the less preferred 2:1 and 1:1 complexes will instead be formed, even if a large excess of hydroxypyrone is present. Under highly basic conditions, poorly soluble gallium hydroxides may precipitate. It is

preferable to regulate the pH with materials other than hydroxides such as sodium hydroxide, as the use of such hydroxides may cause the precipitation of poorly soluble gallium hydroxides, which are not wanted, and the pH may actually be buffered at a low level by this precipitation. The use of a carbonate, especially sodium carbonate, is preferred to regulate the pH. The use of sodium carbonate in a solvent mixture containing ethanol and chloroform, for example, can result in the precipitation of sodium nitrates that are very slightly soluble in this mixture, and which can be filtered off if desired to help purify the solution containing the desired pharmaceutical compositions.

The reaction to form the hydroxypyrone-gallium complex in solution is generally complete within about five minutes at about 20° C. Gentle stirring or other agitation of the solution promotes a uniform, rapid reaction. Longer reaction times may be used if found necessary. Following the separation, if desired, of reaction by-products such as sodium nitrates, sodium chloride, and sodium carbonates (depending on the solvents and reactants used), the reaction mixture may be evaporated slowly in air or, more rapidly, through the use of a rotary evaporator or by freeze drying, as examples. After drying, the gallium complex or complexes will remain in solid form. Recrystallization can be accomplished, if desired, using a suitable solvent, including but not limited to chloroform, alcohols such as ethanol and methanol, ether, water, acetone, and mixtures containing such solvents. Suitable solvents will depend upon which particular gallium complex(es) and impurities are present, upon the impurities to be separated, and upon the temperature and other physical conditions.

It is noted that the mentioned methods are not the only ones that can produce hydroxypyrones and gallium complexes with hydroxypyrones and that various alternative methods may be used as will be apparent to those skilled in the art.

The fluids in mammalian stomachs are generally at a pH below 4, which may cause the less absorbable 2:1 and 1:1 complexes, together with free hydroxypyrone, to predominate when the 3:1 complex reaches the stomach. This situation can be counteracted in several ways, a few of which are mentioned here. One possibility is to mix the 3:1 complex with a suitable buffering agent. Another possibility is to mix the 3:1 complex with an excess of free hydroxypyrone (or a salt thereof containing a physiologically acceptable cation), particularly the one used to make the 3:1 complex. Such a mixture, when dissolved in the stomach, can have the effect of shifting the equilibrium among the 1:1, 2:1, and 3:1 complexes towards a preponderance of the 3:1 complex. Another possibility is formulating or packaging the 3:1 complex in such a way that the dissociation of the 3:1 complex is prevented until the basic conditions of the small intestine are reached. Specific methods include, for example: (1) encapsulating the 3:1 complex in a material that does not dissolve until the small intestine is reached , and (2) formulating the 3:1 complex with certain gels or with other materials that greatly slow the release of the 3:1 complex.

When used for oral administration, the gallium complex may be formulated in a variety of ways. It will preferably be in solid form, and may conveniently be used in compositions containing conventional solid carriers such as lactose, starch, or dextrin, and conveniently presented in tablet or capsule form. Materials and methods to enhance gallium absorption, including those mentioned in the preceding paragraph, may be incorporated. Compositions including a liquid carrier may also be employed for oral administration. To obtain physiologically active gallium levels in the body, compositions for oral administration will likely contain between 0.01 and 20 weight percent gallium complexed with hydroxypyrone in the composition, most likely between 0.5 and 15 weight percent; experiments will be needed to obtain the suitable concentrations for particular applications.

Formulations may also be considered for other modes of administration, for example per rectum, transdermally, and by intravenous, subcutaneous, and intramuscular injection. These formulations may contain a liquid carrier that may be oily, aqueous, emulsified, or contain certain solvents suitable to the mode of administration. Compositions may be formulated in unit dose form, or in multiple or sub-unit doses. The dosage will depend on the medical application, and must be determined by suitable experiments. The compositions will likely contain between 0.001 and 15 weight percent gallium complexed with hydroxypyrone in the composition; experiments will be needed to obtain the suitable concentration for particular applications.

Formulations may also be produced that contain active ingredients other than the gallium complexes. These may include other agents to regulate calcium resorption from bone, for example, but other active agents may also be incorporated.

EXAMPLES

Example 1

Preparation of Gallium Ethyl Maltol

A 1.5M solution of ethyl maltol in chloroform is mixed with an equal volume of a 0.5M solution of gallium nitrate nonohydrate in ethanol to provide a 3:1 molar ratio of ethyl maltol to gallium ions in the mixture. The mixture is stirred for 7 minutes at 22° C. Solid anhydrous sodium carbonate is then added in a 10 molar excess, and stirring continues for an additional ten minutes. When the sodium carbonate is added, a trace of water may sometimes need to be added to facilitate the reaction, which is evidenced by some effervescence. The mixture is then filtered and the filtrate evaporated to give the solid 3:1 complex of ethyl maltol and gallium.

The complex as so produced contains 14.3(1) weight percent gallium by x-ray fluorescence analysis, as predicted for $Ga(C_7H_6O_3)_3$. The material forms white to pale beige monoclinic crystals with unit cell parameters of about a=7.899(1)A, b=8.765(1)A, c=31.626(2)A, beta=103.253(7) degrees, V=2131 A^3, based on powder x-ray diffraction analysis. Crystallization from other solvents or under other conditions may produce other crystal structures.

Example 2

Preliminary Bioavailability Study in Rabbits

As a preliminary test of the oral bioavailability of the 3:1 ethyl maltol:gallium complex, the complex was given to rabbits and compared to a solution of gallium nitrate. Six female New Zealand white rabbits weighing between 2.68 and 2.91 kg were used, and were not fed for 18 hours before starting the experiment. A suspension of the 3:1 gallium ethyl maltol complex in double distilled water was prepared with a concentration of 10 mg elemental gallium per 4 ml of suspension. A solution of gallium nitrate nonohydrate dissolved in double distilled water was also prepared, which had a concentration of 10 mg elemental gallium per 4 ml of solution. A small amount of solid sodium carbonate was added to the latter solution to bring the pH up to about 6. Each of the two solutions was given to three rabbits by oral

gavage (through a tube inserted through the mouth to the stomach) in the amount of 4 ml per kg of body weight, equivalent to 10 mg of elemental gallium per kg of body weight. The stomach tubes were flushed by three ml of water following administration of the solutions.

Six ml of blood was taken from each rabbit at 1 hr, 2 hr, 4 hr, 8 hr, and 24 hr following administration of the solutions, and the serum separated and frozen. Control samples of blood were taken 24 hours earlier. The frozen serum samples were then sent to an independent testing laboratory for determination of the gallium contents by graphite furnace atomic absorption analysis. The testing laboratory received numbered serum samples, and never had any knowledge of the experimental conditions used to produce the samples. The results of the analyses are indicated in Table 1 and on FIG. **1**. Due to uncertainties in the analytical procedures for gallium in serum, the relative proportions of gallium in the serum samples are considered more significant than the actual reported concentrations.

TABLE 1

Mean gallium content of rabbit serum (ng/ml).

	Gallium ethyl maltol suspension (3 animals)	Gallium nitrate solution (3 animals)
pre-treatment	0	0
1 hour	90	51
2 hours	274	99
4 hours	260	118
8 hours	212	103
24 hours	84	64

It is seen from Table 1 and FIG. **1** that the gallium ethyl maltol suspension was absorbed in significantly higher amounts than the gallium nitrate suspension of equal volume and gallium concentration. It is important to note that no attempt was made to counteract the adverse effects of the 3:1 gallium ethyl maltol complex being exposed to the acidic conditions of the stomach. This preliminary study should therefore be considered to give a minimal value for the oral bioavailability of the gallium ethyl maltol complex compared to gallium nitrate.

I claim:

1. A pharmaceutical composition for oral administration to a human individual, comprising, in a solid dosage form, approximately 0.9 to 1800 mg of a neutral 3:1 hydroxypyrone:gallium complex in which the hydroxypyrone is either unsubstituted or substituted with one to three lower alkyl substituents, a pharmaceutically inert carrier suitable for oral drug administration, and, optionally, an additional active agent.

2. The pharmaceutical composition of claim **1** wherein an additional active agent is present.

3. The pharmaceutical composition of claim **2**, wherein the additional active agent is effective to regulate calcium resorption from bone.

4. The pharmaceutical composition of claim **1**, comprising approximately 9 to 360 mg of the neutral 3:1 hydroxypyrone:gallium complex.

5. The pharmaceutical composition of claim **2**, comprising approximately 9 to 360 mg of the neutral 3:1 hydroxypyrone:gallium complex.

6. The pharmaceutical composition of claim **3**, comprising approximately 9 to 360 mg of the neutral 3:1 hydroxypyrone:gallium complex.

7. A pharmaceutical composition for oral administration to a human individual, comprising, in a solid dosage form, approximately 0.9 to 1800 mg of a neutral 3:1 hydroxypyrone:gallium complex in which the hydroxypyrone is selected from the group consisting of 3-hydroxy-4-pyrone, 3-hydroxy-2-methyl-4-pyrone, 3-hydroxy-2-ethyl-4-pyrone, and 3-hydroxy-6-methyl-4-pyrone, a pharmaceutically inert carrier suitable for oral drug administration, and an additional active agent effective to regulate calcium resorption from bone.

8. The pharmaceutical composition of claim **7**, wherein the hydroxypyrone is selected from the group consisting of 3-hydroxy-2-methyl4-pyrone and 3-hydroxy-2-ethyl4-pyrone.

9. The pharmaceutical composition of claim **8**, wherein the hydroxypyrone is 3-hydroxy-2-methyl-4-pyrone.

10. The pharmaceutical composition of claim **8**, wherein the hydroxypyrone is 3-hydroxy-2-ethyl-4-pyrone.

11. The pharmaceutical composition of claim **7**, wherein the carrier is selected from the group consisting of lactose, starch and dextrin.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,048,851
DATED : April 11, 2000
INVENTOR(S) : Lawrence Richard Bernstein

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

In column 1, lines 21-44 should be deleted.

Signed and Sealed this

Thirteenth Day of March, 2001

Attest:

NICHOLAS P. GODICI

Attesting Officer

Acting Director of the United States Patent and Trademark Office